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13. ABSTRACT (Maximum 200 words)

This research program focusses on the brain serotonergic system and its function in relation to integrative physiology and behavior. The primary experimental approaches have employed recording the electrophysiological activity (extracellularly recorded action potentials) of serotonergic neurons and measuring changes in extracellular levels of brain serotonin by means of in vivo brain microdialysis. Somewhat surprisingly, and not expected on the basis of the existing literature, the major variable associated with activation of the brain serotonergic system is tonic and repetitive gross motor activity. Additional studies have explored the connectivity of the brain serotonergic system with other brain systems and the possibility that functional activity in this system induces morphological changes.

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Status of Effort

We have continued to make very good progress in research along a number of lines. We have continued to characterize the activity of brain serotonergic (5-HT) neurons in the various raphe groups in terms of their relation to physiology and behavior. This is our primary line of investigation and where we believe we have made important contributions and had our largest impact. We have also carried out a number of pharmacological studies of these neurons. There are a variety of important aspects to this work since these neuronal groups have been implicated in controlling the organismic stress response, mood, motor activity, circadian rhythmicity, etc. Furthermore, 5-HT neurons are the primary site of action of many therapeutic drugs, such as those used to treat depression and obsessive compulsive disorders. Thus, this work, because of its bearing on the aforementioned issues of mood, motor activity and circadian rhythmicity, is of direct relevance to the AFOSR's mission in neuroscience.

Accomplishments/New Findings

A. Neurophysiology

1. We have now characterized the activity of 5-HT neurons in various raphe groups in relation to motor activity. Virtually all 5-HT neurons in the caudal raphe groups (obscurus and pallidus), which send their projections to the ventral horn of the spinal cord, can be activated during at least one type of motor activity (e.g. locomotion). Some of these neurons can be activated by two or more tasks (e.g. respiration). The types of motor activities are invariably repetitive in nature and are mediated by central pattern generators. 5-HT neurons in the rostral raphe group (dorsalis and medianus), which send their projections into the forebrain, can be even more strongly activated during motor tasks, but this is true of only a subset of them. Furthermore, they can only be activated by motor tasks that are different from those that are effective in the caudal groups, e.g. feeding and grooming.

These data provide the primary support for a new theory in which we have proposed that the primary function of the entire brain 5-HT system is modulation of motor output while secondarily controlling ancillary functions such as sensory information processing and autonomic nervous system activity.

2. We have also found that the activity of brain 5-HT neurons can be phasically decreased during orientation to a novel or strong stimulus. Under these conditions the opposite situation from that described above occurs. The brain 5-HT system is off, motor function is disfacilitated, gross motor output is suppressed, sensory flow is disinhibited, and the organism processes more information. This probably underlies 5-HT's role in memory and learning.
3. In one of our most intriguing experiments we have examined the effect of sleep deprivation on 5-HT neuronal activity. The results are what one would predict if 5-HT's role in antidepressant actions was a general one (it is known to play a key role in all the current antidepressant drugs). As expected, one day of total sleep deprivation significantly activates these neurons, suggesting that 5-HT may play a role

in the well-known antidepressant effects of sleep depriving clinically depressed patients.

4. An additional major role of our research has been to study drugs that control the activity of 5-HT neurons by means of an action at their negative feedback autoreceptor. This is an obvious target for mood altering drugs since they can directly activate or depress 5-HT neuronal activity.
- B. In Vivo Brain Microdialysis (Studies of 5-HT Release)
1. In one of our most important new findings we have shown that the release of 5-HT in various forebrain sites is more strongly tied to behavioral state/motor activity rather than the light-dark or circadian cycle. This finding has enormous implications for 5-HT's role in mood, motor activity, etc.
 2. In a very large, comprehensive study we have found that 5-HT is released in a general manner rather than in a site specific manner throughout the forebrain. We have also found that various stressors are no more effective in increasing 5-HT release than are activating, but non-stressful, conditions.
- C. Morphological Changes
- In an ongoing study in collaboration with Dr. Efrain Azmitia of NYU we are examining whether functional activity can result in morphological changes in the CNS. We know that locomotion strongly activates 5-HT neuronal activity (see above), so here we ask whether it can change the density of innervation of postsynaptic neurons, postsynaptic receptor number, etc.
- D. Afferent Controlling 5-HT Neurons
- In collaboration with Professor Lynn Enquist of Princeton's Molecular Biology Department, we have begun to use retrogradely transported viruses to discover the afferents that control the activity of 5-HT neurons. When 5-HT neuronal activity increases during motor tasks, from where does this message originate? We have begun to answer this question by injecting viruses into motoneuron pools or muscles and then examining which neurons presynaptic to 5-HT neurons contain the virus.

Personnel Supported

Barry L. Jacobs - Professor
Casimir A. Fornal - Senior Research Scientist
Christine Metzler - Research Assistant
Francisco Martin - Postdoctoral Fellow (from Spain)
Lynne Rueter - Graduate Student
James Gardner - Graduate Student
Roger Gallegos - Graduate Student
Jason Radley - Graduate Student
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Publications

- Jacobs, B.L. Serotonin and behavior: A general hypothesis. In: Psycho-pharmacology: The Fourth Generation of Progress. F.E. Bloom and D.J. Kupfer (eds.) Raven Press, New York, 1995, 461-469.
- Jacobs, B.L. and Fornal, C.A. Physiology and pharmacology of brain serotonergic neurons. In: Handbook of Experimental Pharmacology: Serotonergic neurons and 5-HT receptors in the CNS. H.G. Baumgarten and M. Gothert (eds.) Springer (in press).
- Jacobs, B.L. Serotonin, motor activity and depression-related disorders. American Scientist, 1994, 82, 456-463.
- Veasey, S.C., Fornal, C.A., Metzler, C.W. and Jacobs, B.L. Response of serotonergic caudal raphe neurons in relation to specific motor activities in freely moving cats. Journal of Neuroscience, 1995, 15, 5346-5359.
- Jacobs, B.L. and Fornal, C.A. Function of the brain serotonin system. Seminars in Neuroscience, 1995, 7, 401-408.
- Fornal, C.A., Metzler, C.W., Marrosu, F., Ribiero-do-Valle, L.E. and Jacobs, B.L. A subgroup of dorsal raphe serotonergic neurons in the cat is strongly activated during oral-buccal movements. Brain Research, 1996, 716, 123-133.
- Rueter, L.E. and Jacobs, B.L. Changes in forebrain serotonin at the light-dark transition: correlation with behaviour. NeuroReport, 1996, 7, 1107-1111.
- Mendlin, A., Martin, F.J., Rueter, L.E., and Jacobs, B.L. Neural release of serotonin in the cerebellum of behaving rats: An in vivo microdialysis study. J. Neurochem., 1996, 67, 617-622.
- Fornal, C.A., Metzler, C.W., Gallegos, R.A., Veasey, S.C., McCreary, A.C. and Jacobs, B.L. WAY-100635, a potent and selective 5-hydroxytryptamine_{1A} antagonist, increases serotonergic neuronal activity in behaving cats: comparison with (S)-WAY-100135. Journal of Pharmacology and Experimental Therapeutics, 1996, 278, 752-762.
- Rueter, L.E. and Jacobs, B.L. A microdialysis examination of serotonin release in the rat forebrain induced by behavioral/environmental manipulations. Brain Research, 1996, 739, 57-69.
- Marrosu, F., Fornal, C.A., Metzler, C.W. and Jacobs, B.L. 5-HT_{1A} agonists induce hippocampal theta activity in freely moving cats: role of presynaptic 5-HT_{1A} receptors. Brain Research, 1996, 739, 192-200.
- Veasey, S.C., Fornal, C.A., Metzler, C.W. and Jacobs, B.L. Single-unit responses of serotonergic dorsal raphe neurons to specific motor challenges in freely moving cats. Neuroscience (in press).
- Gardner, J.P., Fornal, C.A. and Jacobs, B.L. The effects of sleep deprivation on serotonergic neuronal activity in the dorsal raphe nucleus of the freely moving cat. Neuropsychopharmacology (in press).
- Horvitz, J.C., Stewart, T. and Jacobs, B.L. Burst activity of ventral tegmental dopamine neurons is elicited by sensory stimuli in the awake cat. Brain Research (in press).